

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Kenneth K. Sokoll Confirmation No: 1691
Serial No.: 10/076,674 Examiner: Emily M. Le
Filing Issue Date: February 14, 2002 Group Art Unit: 1648
Title: STABILIZED SYNTHETIC IMMUNOGEN DELIVERY SYSTEM

Mail Stop Appeal Brief
Commissioner of Patents
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Sir:

REPLY BRIEF
PURSUANT TO 37 C.F.R §41.41

Appellant submits this Reply Brief to request that the Appeal be maintained. The period for response is set for within two months from the mailing date of the Examiner's Answer dated July 23, 2008. This response is timely.

STATUS OF CLAIMS is set forth on page **2** of this paper.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL is set forth on page **3** of this paper.

ARGUMENT is set forth on pages **3-10** of this paper.

CLAIMS APPENDIX is presented beginning on page **11** of this paper.

STATUS OF CLAIMS

The Examiner objected to the status of claims as being incorrect and requires the withdrawal claim 10 as not being directed to the elected species.

Although Applicant traverses the requirement, Applicant is willing to comply with the requirement and hereby withdraws claim 10 without prejudice for the purposes of the Appeal. The listing of Claims in the Appendix has been amended to state the status of claim 10 as being withdrawn. The grounds for the traversal are stated below.

Applicant wishes to point out that Claim 10 is dependent on claim 1 now on appeal, and as presented is not patentably distinct from the invention of claim 1.

Claim 1 is directed to a stabilized immunostimulatory microparticulate complex comprising an anionic CpG oligonucleotide and a cationic peptide immunogen. The anionic CpG oligonucleotide is a single stranded DNA comprising 8 to 64 nucleotide bases with a repeat of cytosine-guanidine motif and the number of the CpG motif is in the range of 1-10. It is directed to a combination and is generic.

Claim 10 is directed to a species of the CpG oligonucleotide having the formula: 5'(X³)₂CG(X⁴)₂3' wherein C and CG are unmethylated; and X³ is A or G; and X⁴ is C or T. It is clear that claim 10 is directed to a subcombination and is subgeneric to the invention of Claim 1. Claim 1 reads on the subject matter of claim 1.

Under MPEP §806.05 (a) governing the restriction of a claim directed to a combination (generic) from a claim directed to a subcombination (subgeneric), the claim directed to the subcombination must be patentably distinct from the combination, **and** there must be a serious burden for search.

In the present case, the Examiner has not shown that claim 10 is patentably distinct from the other claims. The combination and subcombination recited have similar uses.

As for the burden of search, it is to be noted that a search for the generic

combination necessarily includes a search for the subgeneric combination. In fact, the prior art the Examiner is relying upon for the grounds for rejection are Krieg et., WO 01/22972, and Ladd et al., WO 94/250560, both of which are supplied by the Applicant in the Information Disclosure Statement (IDS). There is no additional burden for search.

Thus, the requirement to withdraw Claim 10 is improper under MPEP §806.05 (a).

However, for the purposes of the appeal, Applicant now withdraws Claim 10. See the amended Claim Appendix.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Whether the negative inference of other prior art of record, Jones et al., Vaccine, 1999, 17:3065-3071, may be ignored in the process leading to a rejection on the grounds of obviousness.

2. Whether the listing of cancer vaccines in Krieg et al., WO 01/22972, supports the finding of obviousness.

3. Whether Applicant's disclosure may be relied upon for finding inherency to support the finding of obviousness.

ARGUMENT

1. **The Claims Are Not Obvious in view of the Combination of Krieg et al., WO 01/22972, and Ladd et al., WO 94/25060 with Jones et al, Vaccine, 1999, 17:3065-3071.**

The claims of the present application were rejected as being unpatentable under 35 U.S.C. §103(a) as being obvious in view of a combination of Krieg et al., WO 01/22972 and Ladd et al. WO 94/25060. Applicant wishes to point to Jones et al., Vaccine, 1999, 17:3065-3071, as being a part of the prior art of record which was not included in the Examiner's

consideration. The teachings of Jones et al. does not support the finding of obviousness. Under the law, all of the prior art of record must be included in the consideration. [*Layne-New York Company, Inc. v. Allied Asphalt Company, Inc.*, No. 73-1930 (3d Cir., August 15, 1974)]. The lack of consideration of the teachings in Jones et al. is in error.

Jones et al. article, page 3068 stated:

In previous studies, we found that the immune stimulatory effects of ODN containing CpG dinucleotides depended entirely on the bases flanking the CpGs, the number of CpGs in an oligo, and the spacing between the individual motif, the adjuvant effect of CpG ODNs can vary enormously.

Jones et al. also reported that Krieg et al. had found that the flanking bases and spacing between adjacent motifs determined whether a given CpG dinucleotide is stimulatory for a given species (Krieg and Davis, unpublished results). See Jones et al., page 3066, column 1.

Jones et al. disclose that it was necessary to screen several hundred ODNs bearing a wide range of CpG motifs for their mitogenic effect on human cells. They reported that out of this screening they were able to identify two potent ODNs that were effective when mixed with a malarial vaccine peptide immunogen for use in *Aotus* monkeys. Neither Jones et al. nor Krieg et al. teaches nor suggests how to select the appropriate CpG oligonucleotide to be an effective adjuvant for particular peptide immunogens. In contrast, Applicant has provided a way to select effective CpG ODNs that is effective when combines with a cationic peptide immunogens.

The claims of the present application are directed to a combination of an anionic CpG nucleotide with a cationic peptide immunogen, a B cell antigen or a CTL epitope, and a T helper cell epitope to provide a stabilized immunostimulatory microparticulate complex. (Emphasis added). Applicant provides a method of determining whether a CpG oligonucleotide

is anionic and a method of determining whether a peptide immunogen is cationic in order to form the stabilized immunostimulatory microparticulate complex.

Nothing in Krieg et al., Ladd et al., or Jones et al. discloses, describes, teaches or suggests how to stabilize a peptide immunogen. Nothing in Krieg et al., Ladd et al., or Jones et al. discloses, describes, teaches or suggests how to form a stabilized particulate peptide immunogen complex.

Since Jones et al. taught that not all CpG ODN may be effective, there is no motivation to combine Krieg et al. with Ladd et al.

2. The List of Prostate Cancer Vaccines in Krieg et al. Does Not Support the Finding of Obviousness.

The Examiner pointed to the Krieg et al. for the description of mixing CpG oligonucleotides with anti-cancer agents to provide therapeutic agents to support the contention that it is obvious to combine anionic CpG oligonucleotides with cationic peptide immunogens. The Examiner contends that there is motivation to combine an anionic oligonucleotide with a cationic peptide antigen based on the alleged fact that Krieg et al. suggested combining the CpG oligonucleotides described in his patent application with existing prostate cancer immunotherapies.

A review of Krieg et al. shows cancer vaccines listed in Tables D and cancer drugs listed in Table E. Some of the cancer vaccines listed in Table D are identified as “peptide antigens.” However, none of these “peptide antigens” are for prostate cancer. In addition, in Table D, Krieg et al. also describe the cancer vaccines identified as “peptide antigens” as being “encapsulated in liposomal delivery system” or “microsphere delivery system”, suggesting that the peptide antigens are stable and there is no need for stabilization. The CpG oligonucleotides

thus is in an admixture with the cancer vaccines or anti-cancer therapeutic agents as formulated in their existing form which do not complex with the CpG oligonucleotide. The remaining cancer vaccines on the list are viral proteins and are not peptide immunogens.

In Table E, Krieg et al. lists anti-cancer drugs, among which some are identified for the treatment of prostate cancer. The prostate cancer agents in the list are identified as Mitroxanthrone (Immunex), anti-VEGF (Genentech), YM116 (Yamanouchi), and Lodine seeds (Nycomed Amersham). None of which are peptide immunogens. They do not support the Examiner's contention that the cancer immunotherapeutic vaccines or drugs of Krieg et al. render it obvious to combine a specific CpG ODN with Ladd's peptide immunogen, *i.e.*, LHRH conjugated to a T helper cell epitope.

Thus, a careful review of the specification of Krieg et al. does not support the Examiner's contention that it is obvious to combine an anionic CpG oligonucleotide with a cationic peptide immunogen.

3. The Prior Art of Record Does Not Support a Finding of Inherency

The Examiner relied on Krieg et al. and Ladd et al. to support the conclusion of obviousness and the contention that the CpG ODNs of the prior art of record are inherently negatively charged. The Examiner agrees with the Applicant that nowhere in the 156 pages of the specification, the drawings, the Sequence Listing or the 105 claims of Krieg et al. is the term "anionic" or the phrase "net negative charge" to be found. Additionally, nowhere in Krieg et al. is there a way of selecting an appropriate CpG oligonucleotide to form a stable, microparticulate complex with a peptide immunogen.

The Examiner pointed to Krieg et al. for identifying SEQ ID NO:429 in Table A which listed 1097 CpG oligonucleotides as being effective for adjuvant purposes. The Examiner stated that since SEQ ID NO:429 is identical to SEQ ID NO:1 of the present application and the Applicant disclosed that SEQ ID NO:1 is anionic with a charge of -32, SEQ ID NO:429 of Krieg et al. is inherently anionic with a charge of -32. However, the Examiner admitted that Krieg et al. does not teach, describe, or suggest that SEQ ID NO:429 is negatively charged at a pH of 5.0-8.0.

Nothing in the prior art of record supports the Examiner's contention that this property is allegedly recognized by one of skill in the art as being inherent to CpG ODNs. Neither Krieg et al. nor Jones et al. concerned with CpG ODNs mentioned this characteristic. Thus, the Examiner's contention that SEQ ID NO:429 is inherently anionic relies solely on the disclosure of Applicant's application. As pointed out and admitted by the Examiner, this is not the law. Inherency must be proven by evidence at hand such as the prior art of record at the time the Applicant conceived of the invention. Inherency cannot be found by applying Applicant's own teaching. The prior art of record does not disclose the claimed invention. Whereas, only the Applicant disclosed that the CpG oligonucleotide of the claimed invention is negatively charged at a pH of 5.0-8.0 due to the phosphorothiorate moieties attached to SEQ ID NO:1.

In fact, Krieg et al. teaches that some ODNs are immunostimulatory and some are not. Only by testing each ODN can one confirm the ability of the ODN to be immunostimulatory. See page 130 of Krieg et al. According to Krieg et al., the stimulatory effects are due to the presence of TG and not those of a phosphorothioate backbone. Based on this statement, Krieg et al. teaches against the addition of phosphorothioate moiety or a

thiolacetamido glycopolymer to the backbone of a CpG oligonucleotide.

a. **Ladd et al. WO 94/25060 Does not Support a Finding of Inherency**

Ladd et al. describes LHRH conjugated to a T helper cell epitope for sterilizing an animal. It also discloses that the LHRH conjugated to T helper cell epitope may be used in the treatment of enlarged prostate or prostate cancer. There is no disclosure, teaching or suggestion, however, of the LHRH-T helper cell epitope combination as being cationic at a pH of 5.0 to 8.0 and forming a stable microparticulate complex with anionic CpG oligonucleotides. Only when one recognizes that specific CpG ODNs are negatively charged due to the presence of a phosphodiester, such as a phosphorothiorate moiety, would one be motivated to identify, select, or form cationic peptide immunogens. The disclosure of Ladd et al. does not provide such a motivation. In fact, there is no discussion in Ladd et al. of the instability of peptide immunogens nor any teaching or suggestion as to how to stabilize the immunogen or how a peptide immunogen may be rendered cationic.

The Examiner's burden to prove *prima facie* obviousness must be based on the evidence provided in the prior art of record. There is nothing in Krieg et al. with respect to the combination of an anionic CpG oligonucleotide with a cationic peptide comprising a B cell epitope or a CTL epitope and a T helper epitope. Moreover, there is nothing in Krieg et al. with respect to determining if a peptide is cationic or how to render a peptide cationic. Furthermore, there is nothing in Ladd et al. about a cationic peptide nor how to render a peptide to be cationic. Ladd et al. does not disclose, teach, or suggest what makes a peptide cationic nor how to make a peptide cationic by adding a lysine, arginine or histidine to its N- or C-terminal.

b. The Finding of Inherency is based on Impermissible Hindsight

To counter Applicant's citation of *KSR* for impermissible hindsight, the Examiner stated on page 20 of the Answer:

[i]t must be recognized that any judgment on obviousness is in a sense necessarily reconstruction based on hindsight reasoning.

The Examiner concedes that hindsight reconstruction is acceptable only

[i]f it takes into account only knowledge which was within the level of ordinary skill in the art at the time the invention was made and does not include knowledge gleaned only from the Applicant's disclosure, such a reconstruction is improper.

In the present case, the Examiner concluded that SEQ ID NO:429 has a negative charge of -32 when nothing in the prior art of record shows that a person of ordinary skill would recognize this without Applicant's disclosure. The Examiner also concluded that SEQ ID NO:35 of Ladd et al. has a positive charge because it is identical to SEQ ID NO:9 of the present application. Without Applicant's disclosure, a person of ordinary skill in the art would not recognize that SEQ ID NO: 35 is positively charged at a specified pH from Krieg et al., Ladd et al. or Jones et al. Thus, the Examiner's hindsight reconstruction is based on knowledge gleaned from Applicant's disclosure and is improper and should be reversed.

CONCLUSION

In view of the foregoing, Appellant respectfully submits that neither the Final Office Action nor the Examiner's Answer has met the burden for proving *prima facie* obviousness in the rejection of claims 1, 4-19, 12-13 and 18-19. The finding of obviousness was made applying the teachings of Applicant's specification and should be reversed. Appellant therefore requests that the Board reverse the rejections in the Final Office Action and direct the Examiner to withdraw the Office Action and allow claims 1, 4-19, 12-13 and 18-19.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be associated with the filing of this paper, or credit any overpayment, to Deposit Account No. 13-4500, Order No. 1151-4172.

Respectfully submitted,



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CLAIMS APPENDIX

1. (Amended) A stabilized immunostimulatory microparticulate complex comprising a cationic peptide immunogen wherein the peptide immunogen comprises a target B cell antigen or a CTL epitope and a T helper cell epitope and an anionic CpG oligonucleotide wherein the cationic peptide immunogen has a net positive charge at a pH in the range of 5.0 to 8.0 calculated by assigning a +1 charge for each lysine (K), arginine (R) or histidine (H), a -1 charge for each aspartic acid (D) or glutamic acid (E) and a charge of 0 for all other amino acids in the peptide immunogen and wherein the anionic CpG oligonucleotide has a net negative charge at a pH in the range of 5.0-8.0 and is a single-stranded DNA comprising 8 to 64 nucleotide bases with a repeat of a cytosine-guanidine motif and the number of repeats of the CpG motif is in the range of 1 to 10.

2-3. (Canceled)

4. The immunostimulatory microparticulate complex of claim 1, wherein the cationic peptide immunogen is a mixture of synthetic peptide immunogens.

5. The immunostimulatory microparticulate complex of claim 1, wherein the net positive charge of the cationic peptide immunogen is at least +2.

6. The immunostimulatory microparticulate complex of claim 4, wherein the average net positive charge of the mixture of synthetic peptide immunogens is at least +2.

7. The immunostimulatory microparticulate complex of claim 5 or 6, wherein the net negative charge of the anionic oligonucleotide is at least -2.

8. The immunostimulatory microparticulate complex of claim 1, wherein the CpG oligonucleotide is a single-stranded DNA molecules with 18-48 nucleotide bases and the number of repeats of CpG motif therein in the range of 3 to 8.

9. The immunostimulatory microparticulate complex of claim 1, wherein the CpG oligonucleotide has the formula: 5' X¹CGX² 3' wherein C and G are unmethylated; and X¹ is selected from the group consisting of A (adenine), G (guanine) and T (thymine); and X² is C (cytosine) or T (thymine).

10. (Withdrawn) The immunostimulatory microparticulate complex of claim 1, wherein the CpG oligonucleotide has the formula: 5'(X³)₂CG(X⁴)₂ 3' wherein C and G are unmethylated; and X³ is A or G; and X⁴ is C or T.

11. (Cancelled)

12. The immunostimulatory microparticulate complex of claim 1, wherein CpG oligonucleotide is selected from a group consisting of 5' TCG TCG TTT TGT CGT TTT GTC GTT TTG TCG TT 3' (CpG1) SEQ ID NO: 1, a 32 base length oligomer, and 5'nTC GTC GTT TTG TCG TTT TGT CGT T 3' (CpG2) SEQ ID NO: 2, a 24 base length oligomer plus an phosphorothioate group designated as n.

13. The immunostimulatory microparticulate complex of claim 12, wherein CpG oligonucleotide is 5' TCG TCG TTT TGT CGT TTT GTC GTT TTG TCG TT 3' (CpG1) SEQ ID NO: 1.

14.-17. (Withdrawn)

18. The immunostimulatory microparticulate complex of claim 12, wherein the cationic peptide immunogen is a synthetic peptide is conjugated to a T helper cell epitope.

19. The immunostimulatory microparticulate complex of claim 18, wherein the cationic immunogen is selected from the group consisting of SEQ ID NO: 7, 8 and 9 and a mixture thereof.

20. -75. (withdrawn)

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EVIDENCE APPENDIX

None.

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RELATED PROCEEDINGS APPENDIX

None.